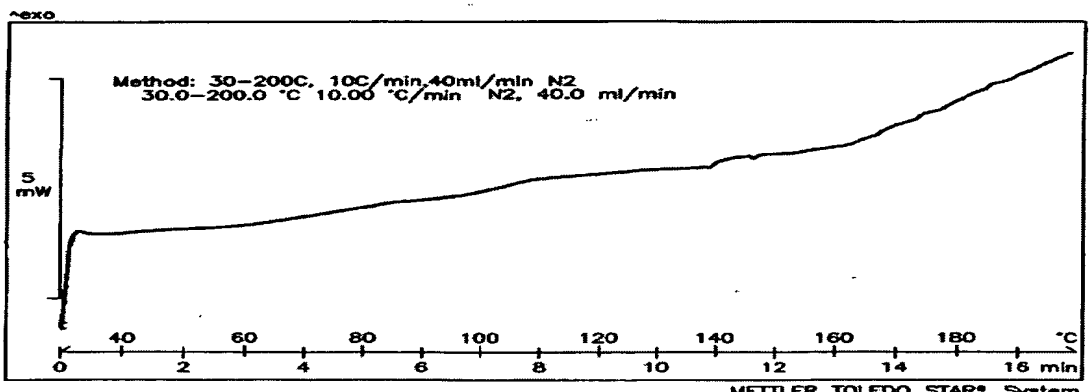
**REMARKS/ARGUMENTS**

The undersigned thanks the supervisory Examiner Joseph McKane for interview of July 17, 2006. The undersigned was present with one of the inventors of the present application, Judith Aronhime. Patentability of the claims was discussed in light of the '578 patent.

An agreement was reached to file an RCE. The parties agreed that the claim contained allowable subject matter and following an RCE, the claims might need to be amended for clarity. Additionally, claim 18 would be reintroduced.

The claims have been amended to recite "melting enthalpy" instead of "melting point." Differential Scanning Calorimetry (DSC) monitors heat effects associated with phase transitions. In this technique, a sample and a reference material are subject to a controlled temperature program. When a phase transition such as melting occurs in the sample, an input of energy is required to keep sample and reference at the same temperature. This difference in energy is recorded as a function of temperature to produce the DSC thermogram. Therefore the term "melting enthalpy" is more appropriate because it reflects the energy state of the system.

The following DSC thermogram (Figure 3 of the application) is that of the amorphous valsartan of the present invention:




DSC curve of Valsartan purely amorphous.

Fig. 3

This DSC thermogram is flat and lacks a melting enthalpy.

The Office Action rejects the claims under Section 103 in light of the '578 patent by Buhlmayer et al. The '578 patent prepares valsartan in examples 16 and 37. The melting point provided for the valsartan of Example 37 is 116-117°C. The '578 patent is silent as to which method it uses to measure a melting point. In light of the silence, one of ordinary skill of art would consider that the melting point was taken visually with a capillary tube since such method is the standard laboratory practice. As evident, this melting point is well defined and narrow in range, which is characteristic of a crystalline material.

The melting range provided for the product of Example 16 is 105-115°C. In the previous Office Action, the undersigned stated:

> **According to the Office Action, the '578 patent discloses valsartan with a melting point of 105 to 115°C. ('578 patent, col. 34, l. 62). Because it exhibited a melting point, that valsartan was at least partially crystalline, and not completely amorphous.**

This statement does not take into account that a melting range can be measured visually with a capillary tube; the undersigned apologizes for any confusion caused by it.

The '578 patent does not characterize its solid as amorphous or crystalline, but a later filed application by an inventor of the '578 patent references this example. Specifically, Example 16 is mentioned in a PCT application which published as WO02/06253. Buhlmayer, the first named inventor of the '578 patent, is listed as an inventor on the face of this PCT application.

The PCT application states:

> The active ingredient valsartan is the free acid which is described specifically in EP 0443983, especially in Example 16.

EP 0443983 is equivalent to the '578 patent, and has the same Example 16.

Two paragraphs after citing Example 16, the PCT application states:

> The free acid valsartan has a melting point in a closed crucible of 80 to 95°C and in an open crucible of 105 to110°C and amelting enthalpy of 12 kJ/mol.

The PCT application then states:

> The X-ray diffraction diagram consists essentially of a very broad, diffuse Xray reflection; the free acid is therefore characterised as almost amorphous under X-ray. The melting point linked with the measured **melting enthalpy** of 12kJ/mol unequivocally confirm the existence of a considerable residual arrangement in the particles or structural domains for the free acid valsartan.

(emphasis added). Thus, a PCT application by an inventor of '578 patent states that the valsartan acid of the art exhibits an enthalpy of 12KJ/mole.

Valsartan has a mass of 435g/mole. 12000J/mole divided by 435g/mole is about 28 J/g. The present claims are directed to valsartan lacking a melting enthalpy above about 1 J/g. As apparent, the claimed product of the present invention is different than that of the art.

According to M.P.E.P. § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." *See also In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999).

A *prima facie* case of obviousness has not been established since there was no suggestion in the art on how to prepare amorphous valsartan lacking a melting enthalpy in the DSC, and there was certainly no reasonable expectation of success of preparing such amorphous valsartan. Polymorphism and polymorph generation is an unpredictable art: "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." H.G. Brittain, "Polymorphism in Pharmaceutical Solids," p. 185 (Marcel Dekker 1999). Finally, the prior art references do not teach or suggest the limitation of valsartan lacking a melting enthalpy in the DSC.

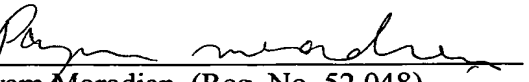
During the interview, supervisory Examiner Joseph McKane "agreed that the claim contained allowable subject matter." It is respectfully submitted that the amendment of the claims to recite the term "melting enthalpy" puts these claims in condition for allowance.

During the interview, it was also agreed that claim 18 would be reintroduced. Claim 18 has been reintroduced as an independent claim, specifically claim 83, and recites "Amorphous valsartan having a DSC thermogram that lacks a melting enthalpy above about 1 J/g in region of about 80°C to about 100°C in said DSC." As discussed during the interview, a DSC analysis is generally carried out in a closed crucible. The PCT application discloses that the amorphous valsartan of the art had a closed crucible melting point in the region of 80 to 95°C. This claim explicitly states that a melting enthalpy is lacking in the region that such melting enthalpy should other wise exist. Claims 84-94 have been also added, which directly or indirectly mimic the other withdrawn dependent claims, but incorporate the feature of claim 83 instead of claim 17.

Allowance of the two pending claims (83 and 17) is appreciated. If these claims are deemed allowable, rejoinder of the rest of the claims would be appreciated. All of the other claims depend from or otherwise require all the limitation of at least one of these two claims. MPEP 821.04.

Having addressed all the outstanding rejections and objections, Applicants submit that the application is in a condition for allowance. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully submitted,
KENYON & KENYON

Dated: September 8, 2006 By: 
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